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CONSENSUS STATEMENT

Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology

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Abstract

Objective We developed clinical practice guidelines to assess the individual risk–benefit profile of androgen replacement therapy in adult male hypogonadism (HG), defined by the presence of specific signs and symptoms and serum testosterone (T) below 12 nmol/L.

Participants The task force consisted of eight clinicians experienced in treating HG, selected by the Italian Society of Endocrinology (SIE). The authors received no corporate funding or remuneration.

Consensus process Consensus was guided by a systematic review of controlled trials conducted on men with a mean $T < 12$ nmol/L and by interactive discussions. The guidelines were reviewed and sequentially approved by the SIE Guidelines Commission and Executive Committee.

Conclusions We recommend T supplementation (TS) for adult men with severely reduced T levels ($T < 8$ nmol/L)

to improve body composition and sexual function. We suggest that TS be offered to subjects with $T < 12$ nmol/L to improve glycaemic control, lipid profile, sexual function, bone mineral density, muscle mass and depressive symptoms, once major contraindications have been ruled out. We suggest that lifestyle changes and other available interventions (e.g. for erectile dysfunction) be suggested prior to TS. We suggest that TS should be combined with currently available treatments for individuals at high risk for complications, such as those with osteoporosis and/or metabolic disorders. We recommend against using TS to improve cardiac outcome and limited mobility. We recommend against using TS in men with prostate cancer, unstable cardiovascular conditions or elevated haematocrit. The task force places a high value on the timely treatment of younger and middle-aged subjects to prevent the long-term consequences of hypoandrogenism.

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Methodology and definitions

The recommendations were based exclusively on evidence from randomised controlled trials (RCTs) of hypogonadal (HG) subjects, defined by a mean serum testosterone (*T*) level below 12 nmol/L. Data from undefined and mixed populations (eugonadal/HG) or from non-RCTs were analysed separately and taken into account for the formulation of values and remarks only.

A number of problems were encountered in the reviewing process. These pertained to: (a) poor biochemical and clinical definition of HG in the inclusion criteria; (b) variability in the age of enrolled subjects, with the majority of studies performed in middle-aged subjects (below 75 years); (c) variability in *T* formulation and dose, ranging from suboptimal to supra-physiological regimens; (d) inconsistencies in the definition of comorbidities (especially for metabolic and cardiovascular disorders); (e) extreme variability in the duration of treatment (from 4 weeks to 36 months); (f) heterogeneity in the methods for assessing the primary outcomes; (g) no study primarily designed to assess cardiovascular or prostate outcomes; (h) study duration insufficient to address cardiovascular and prostate safety; (i) unstated or underpowered sample sizes for either the primary or secondary outcomes for most studies.

The task force used the following coding system: (1) indicates a strong recommendation and is associated with the phrase “we recommend”; (2) denotes a weak recommendation and is associated with the phrase “we suggest.” Evidence grading: ØØØØ denotes very low quality evidence; ØØØØ, low quality; ØØØØ, moderate quality; and ØØØØ, high quality.

The term *T* replacement therapy has been shortened to TS. For all recommendations, when not otherwise specified, HG was defined as mean circulating *T* levels below 12 nmol/L and the presence of specific signs and symptoms, reviewed as potential outcomes: reduced muscle mass and increased adiposity, altered glucose metabolism, reduced bone density, low libido, erectile dysfunction, depression, HIV-related muscle wasting, impaired exercise capacity and anaemia. The formulated recommendations do not apply to men with mean *T* values above 12 nmol/L.

Metabolic outcomes

1. We suggest TS for HG subjects with metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) to improve glycaemic control (2 ØØØØ).
2. We suggest TS for HG subjects to improve lipid profile (2 ØØØØ).

3. We recommend TS to reduce fat mass in HG subjects (1 ØØØØ), and we suggest it for subjects with either MetS or T2DM (2 ØØØØ).
4. We suggest TS to increase lean mass in HG subjects (2 ØØØØ) and in those with MetS and T2DM (2 ØØØØ).
5. We suggest TS to reduce waist circumference in HG subjects with MetS and T2DM (2 ØØØØ).

Evidence

In HG subjects with MetS and/or T2DM, a limited number of studies show a tendency towards improved glycaemic control after TS [1]. However, this trend is not evident in the general HG population [2–4] and is less evident in MetS. Conversely, lipid profile, which is tested in a higher number of studies, seems to improve after TS in all HG patients [5–8], but this is not so evident in HG subjects with MetS and/or T2DM [9–11]. Body mass index (BMI) is not affected by TS in HG subjects with or without metabolic disorders [3, 9, 10]. A clear-cut decrease in fat body mass during TS is reported in almost all studies performed in unselected HG subjects [12] and in the fewer studies performed in HG patients with MetS and/or T2DM [9–11, 13, 14]. Similarly, lean mass increases in all HG patients receiving TS, although the trend is less evident in patients with dysmetabolism.

Value

We place an important value on changes to body composition and metabolic profile in men with unequivocally reduced *T* levels.

Remarks

Although the efficacy of TS in improving body composition has been consistently replicated, the task force remarks that TS should not be administered as an alternative to appropriate lifestyle changes [15], which should be pursued prior to or, in selected cases, alongside TS.

Bone outcomes

6. We suggest TS in men with reduced *T* levels to improve, or avoid worsening of, lumbar (2 ØØØØ) and femoral (2 ØØØØ) bone mineral density.

Evidence

T has a fundamental role in bone maturation: at the end of puberty to reach peak bone mass, and during adult life to

maintain it [16]. HG men have significantly lower bone mineral densities (BMD) than eugonadal age-matched men [16]. The prevalence of HG in osteoporotic men, however, has not been properly assessed. Studies estimate HG in up to 20 % of men with vertebral fractures and 50 % of hip fractures [17]. Some non-placebo-controlled trials and/or trials in strictly selected non-HG men without other major comorbidities are available [18–22]. Taken together, these studies suggest a positive effect of TS on lumbar spine but not femoral neck BMD. Only two RCTs [23, 24] have been conducted in elderly and clearly HG men ($T < 12$ nmol/L), for a total of 41 subjects [23, 24], treated with intramuscular *T* injection. These studies show a significant effect of TS on femoral BMD, as compared to placebo (+2.7 %) [23, 24], and a more pronounced effect (+10.2 %) on lumbar BMD, after 36 months [23]. Another controlled study, performed on 99 HG men with a history of fracture or *T*-score < -2.0 and frailty, shows a positive effect of transdermal TS on lumbar BMD [20]. One non-placebo-controlled RCT study performed on 40 HG men with sexual symptoms and MetS or T2DM shows a positive relationship between serum *T* and BMD increments at both the lumbar and femoral sites after 36 months of *T* undecanoate treatment [18].

Values

Evidence supporting TS to increase lumbar BMD in HG men is of low quality. The evidence for femoral BMD is of very low quality. The task force places a high value on the long-term (36 months) composite benefits of TS on the musculoskeletal system, especially when *T* levels are very low (< 8 nmol/L).

Remarks

Although there is no doubt that *T* is a key hormone for skeletal health, a careful diagnosis should be made to characterise HG, excluding other causes of low BMD and understanding the relative role of other comorbidities, especially in men with only a marginal reduction in *T* levels. No studies report effects on fracture rates after TS, nor is there any evidence for the effects of co-treatment with agents with proven anti-fracture efficacy (e.g. bisphosphonates) and/or vitamin D/calcium supplementation. Similarly, there is no clear evidence of better results with *T* injections than with transdermal administration. For this reason, the task force suggests adding other pharmacological agents to treat osteoporosis if the fracture risk is high. Men with a modest or borderline risk of fracture can be treated with TS alone. In general, the decision on if and when to add vitamin D, calcium and/or another specific treatment and which *T* formulation to use should be based on an assessment of the risks and benefits for the patient concerned.

Cardiovascular outcomes

7. We suggest that clinicians exercise caution in giving *T* to older men with known cardiovascular disease (CVD), due to an unclear benefit/risk ratio (2 ØØØØ).
8. In patients deserving treatment, we suggest offering long-acting injectable *T* esters or transdermal preparations rather than short-acting *T* esters, to minimise the risk of increased haematocrit, a potential cardiovascular risk factor (2 ØØØØ).
9. We suggest considering TS for middle-aged HG men with metabolic disorders without known CVD, to decrease the risk of future cardiovascular events (2 ØØØØ).
10. We recommend against TS to improve cardiac dysfunction in HG men (1 ØØØØ).

Evidence

The effects of TS on cardiovascular function, events and mortality of HG patients are poorly known [25]. Some studies show beneficial effects on surrogate markers of cardiovascular health [8, 14, 26]. The few RCTs and subsequent meta-analyses [27–29] suggest that TS in men is not associated with a consistent CV effect. Most trials rely on too few adverse events to reach reliable conclusions. A recent meta-analysis of RCTs [30] identified 27 trials including 2,994 middle-aged or elderly men (1733 *T*-treated) with a baseline *T* level ranging between 7.0 and 20.0 nmol/L, reporting 180 CV-related events, including CV-related deaths. *T* treatment increased the risk of CV-related events (OR 1.54, 95 % CI 1.09–2.18), including CV-related deaths (OR 1.42; 95 % CI 0.70–2.89), independently of baseline *T* level [30]. However, a more recent meta-analysis [31] on a much larger population (5,508 men, 3,040 treated with *T*) confutes these findings, showing no effect on major cardiovascular events (MACE) and mortality, and a somewhat CV-protective effect in a subgroup of HG men with metabolic diseases (OR 0.19 95 % CI 0.04; 0.85). The major limitation is that none of these RCTs had CV function or events as the primary or secondary outcome, and all studies were underpowered to address this issue. In addition, reporting of adverse events, bias linked to trial funding [30, 32] and study duration too short to define CV safety all undermine the validity of the currently available data. A qualitative review of the trials seems to suggest that long-acting injectable *T* esters or transdermal preparations should be preferred to reduce the risk of excessive haematocrit increase during TS [28, 33], although a formal quantitative appraisal is still lacking [30].

Values

The recommendation to offer TS to elderly HG men places a relatively low value on avoiding the burden of TS and its unclear cardiovascular effects.

Remarks

The risks of treating elderly HG men with TS appear to be related to age, history of previous CV events and rise in haematocrit. In younger and middle-aged HG subjects [34], these risk factors seem, on the whole, to play a minor role compared to the potential benefits of TS in reducing several other cardiovascular risk factors.

Sexual function

11. We recommend TS for men with symptoms of low libido who have markedly reduced T levels ($T < 8$ nmol/L) to improve libido (1 ØØØØ); whilst we suggest TS in men with T levels between 8 and 12 nmol/L (2 ØØØØ).
12. We recommend that clinicians offer TS to men with erectile dysfunction (ED) who have markedly reduced T levels ($T < 8$ nmol/L), to improve erection (1 ØØØØ).
13. In men with T levels between 8 and 12 nmol/L and ED, we suggest considering TS after having tried the established therapies to recover sexual function (2 ØØØØ). In non-responders to phosphodiesterase 5 (PDE5) inhibitors who retain persistently low T levels, we suggest offering T therapy to improve erectile function (2 ØØØØ).
14. We suggest that clinicians offer TS to men with low T levels ($T < 12$ nmol/L) to improve orgasmic function (2 ØØØØ).

Evidence

Observational data show that sexual complaints, including ED, are the most common symptoms associated with HG [35, 36]. Simple correlation, however, does not imply causation. Several non-placebo-controlled trials are available [37–40]. The few RCTs contain a sufficiently large number of treated subjects to draw reliable conclusions [37–39]. The effects of TS on libido have recently been meta-analysed [38]. In 17 RCTs, enrolling 1,111 men, TS determined an improvement in the libido of severely HG subjects ($T < 8$ nmol/L), but not in those with milder forms of HG. The effects of TS on sex-related erections were assessed in 1,431 individuals, proving effective only in men with reduced T levels (< 12 nmol/L) [38]. An

inverse relationship between mean T levels at enrolment and the effect of TS on overall erectile function was observed. Amongst studies providing International Index of Erectile Function (IIEF) data, TS resulted in a weighted mean improvement of about 40 % (range: 22–79 %), corresponding to a weighted mean delta of 4 ± 2 points in the IIEF-5 score (range: 3–8) [39]. Clinical studies document that T not only controls libido and erectile function but is also involved in the regulation of the orgasmic component of male ejaculatory reflex, acting both centrally and peripherally [38]. Ten studies enrolling 677 patients investigated the effect of TS on orgasm, confirming the relationship between baseline mean T levels and the effect size on TS orgasmic function.

Values

There is enough evidence to support the use of TS for men with unequivocally low T levels and sexual complaints. The task force places a high value on the composite benefits of treating young HG men and a lower value on the treatment of older men, due to the uncertainty of long-term CV safety.

Remarks

The decision as to whether or when to treat HG men to improve sexual symptoms remains problematic. ED generally has a multifactorial aetiology; vascular factors are predominant amongst the comorbidities and hamper the beneficial effects of TS. In young HG subjects, TS is often sufficient to improve sexual function. In older men, the low T level may be the consequence rather than the cause of ED [41]. A large number of HG ED patients could be safely treated with PDE5-I monotherapy and TS could be offered as an add-on treatment only for those with persistently low T levels, [39, 41]. The decision to start TS in older HG men depends on the patient's individual benefit/risk ratio.

Other outcomes

15. We suggest that clinicians offer TS to HG men with depression to improve depressive symptoms (2 ØØØØ), in addition to the established therapies for depression.
16. We suggest that clinicians offer TS to HG men and HIV/AIDS to improve lean mass (2 ØØØØ).
17. We suggest against the use of TS to improve exercise capacity in individuals with chronic obstructive pulmonary disease (COPD) and frail men (2 ØØØØ) or to improve quality of life (QoL) in subjects with end-stage renal diseases (ESRD) or undergoing glucocorticoid or opioid therapy (2 ØØØØ).

Evidence

Depression

Depressed mood is a symptom often associated with HG, suggesting that androgen deficiency contributes to mood disorders [1, 42, 43]. It is unclear, however, whether low *T* levels are correlated with the development of major depressive disorder [42]. The relationship between low *T* and the incidence of clinical depression is still unclear, especially in elderly men [42]. Few RCTs have evaluated the effect of TS on depressive symptoms (Table 1). Zarrouf et al. [43] evaluated the impact of TS on major depressive disorder according to DSM-IV-defined criteria in seven trials including 355 patients with an age range of 18–70 years. They found a positive effect of TS on Hamilton-D depression rating scale scores in depressed patients with *T* < 10 nmol/L and in patients with HIV/AIDS. Similar results are reported in a more up-to-date meta-analysis [44].

HIV/AIDS

The prevalence of low *T* levels in HIV-infected men ranges from 20 to 25 % [1, 45, 46]. Low *T* is closely correlated with weight loss, progression to AIDS, wasting syndrome, depression and loss of muscle mass and exercise capacity [45]. The mechanisms underlying the association between HG and HIV have been reviewed elsewhere [45]. In a recent meta-analysis of the available RCTs in HIV-positive men, including 344 individuals, Corona et al. [1] found that TS improved lean mass over placebo. However, results from these trials were heterogeneous and limited by the small sample size. In particular, when more selective criteria for HG were applied (*T* < 12 nmol/L) only two trials were eligible (Table 1).

Other diseases

Current guidelines [47, 48] suggest that clinicians consider case detection through measuring total *T* levels in men with certain clinical conditions (including CPOD, ESRD or in those treated with opioid or glucocorticoid therapy). However, the limited evidence from RCTs in these particular populations does not permit any final conclusions to be drawn about the specific role of TS in these subjects or in frailty [1].

Values

The task force places a relatively high value on the recommendation to offer TS to HG men with major depressive disorders and in those resistant to the use of common

antidepressants, and a high value on TS in HIV-infected men with HG to prevent and/or combat wasting syndrome by improving lean body mass.

Remark

It should be recognised that evidence for the role of TS in depressed or HIV men is limited, considering both the number of patients enrolled and the follow-up. Further information on the long-term benefits and adverse effects of *T* use in these subjects is therefore required. The outcomes of TS in other disorders, including CPOD and ESRD, in frail subjects or in those treated with glucocorticoids or opioids are the same as for patients with classic androgen deficiency [47, 48].

The prostate

18. We recommend against limiting TS in HG men with the aim of preventing a new incidence of prostate cancer (PCa) (1 ØØØØ).
19. We recommend against using TS in HG men with PCa and we recommend against using TS, without further urological investigation, when total PSA is above the normal or in the presence of an abnormal digital rectal examination (palpable nodule) (1 ØØØØ).
20. We suggest considering TS in men with signs and symptoms of HG after at least 12 months of clinical and biochemical cure following radical prostatectomy for PCa, but only under strict monitoring (2 ØØØØ).
21. We suggest against using TS in HG men with an overt urinary tract obstruction due to benign prostatic enlargement (BPE) (2 ØØØØ).
22. We recommend long-term follow-up in men with markedly low (<8 nmol/L) or borderline (8–12 nmol/L) *T* levels and symptoms of HG who are given TS; this should be stricter in the first year [3, 6 (or 9 according to the clinician's judgement) and 12 months] and at least annually thereafter, with measurement of total (and free) PSA and evaluation of prostate volume by digital rectal examination (1 ØØØØ) or trans-rectal ultrasound.

Evidence

There are no data suggesting that TS is associated with an increased risk of prostate cancer [49]. Observational data on >1,100 subjects revealed that about 64 % of HG men treated with *T* do not show an increase in PSA. Six RCTs found that TS increases PSA values [6, 23, 50–53], but only in two was the increase significant [52, 53]. The

Table 1 Evidence from available RCTs in support of the provided recommendations

Characteristics of study population	Outcome	Number of available RCTs	Number of enrolled subjects	Mean duration of RCT months (range)	Summary of observed effects
Body composition (for additional data see references [1–15])					
MetS or T2DM	Waist circumference	6	701	10.7 [2.7–24]	↓
Metabolically unclassified	Waist circumference	3	172	6.6 [3–11]	↔
MetS or T2DM	BMI	8	773	8.8 [2.7–24]	↔
Metabolically unclassified	BMI	5	307	11.2 [3–24]	↔
MetS or T2DM	Body fat	5	379	10.7 [3–24]	↓
Metabolically unclassified	Body fat	10	1,513	11 [3–36]	↓
MetS or T2DM	Body lean	4	174	10.4 [2.7–24]	↑
Metabolically unclassified	Body lean	9	1,491	10.8 [3–36]	↑
Metabolism (for additional data see references [1–15])					
MetS or T2DM	Glycaemia	7	725	9.6 [2.7–24]	↔
Metabolically unclassified	Glycaemia	5	324	9.4 [3–24]	↔
MetS or T2DM	Glycated haemoglobin	6	555	10 [2.7–24]	↓
MetS or T2DM	Total cholesterol	7	725	9.6 [2.7–24]	↔
Metabolically unclassified	Total cholesterol	9	490	11.7 [1–36]	↓
MetS or T2DM	HDL cholesterol	7	725	9.6 [2.7–24]	↔
Metabolically unclassified	HDL cholesterol	10	546	13 [1–36]	↔
MetS or T2DM	LDL cholesterol	5	633	6.2 [2.7–12]	↔
Metabolically unclassified	LDL cholesterol	8	464	15.5 [1–36]	↓
MetS or T2DM	Triglycerides	7	725	9.6 [2.7–24]	↔
Metabolically unclassified	Triglycerides	8	380	8.7 [1–36]	↓
Bone density (for additional data see references [16–24])					
Healthy men	Lumbar and femoral bone mineral density	2	41	12–36	↑ lumbar ↑ femoral
History of fracture or <i>T</i> -score <−2.0 and frailty	Lumbar, femoral and radius bone mineral density	1	53	12	↑ lumbar ↓ radius
Sexual function (for additional data see references [35–41])					
Young to middle-aged men with sexual dysfunction	Libido	17	1,111	3 months (1–12)	↑ (if <i>T</i> < 8 nM/L)
Young to middle-aged men with sexual dysfunction	Sexual related erections	24	1,431	3 months (1–12)	↑ (if <i>T</i> < 12 nM/L)
Young to middle-aged men with sexual dysfunction	Orgasmic function	10	677	3 months (1–12)	↑ (if <i>T</i> < 12 nM/L)
Prostate gland (for additional data see references [6, 9, 10, 23, 49–55])					
Middle-aged to aged men with hypogonadism	Serum PSA	6	286	16.5 [3–36]	↔
Men with hypogonadism (unspecified age or wide age range)	Serum PSA	10	461	6 [3–12]	↔
Middle-aged men with hypogonadism	Prostate volume or prostate-related symptoms (DRE and evaluation of low urinary tract function)	7	256	10 [3–36]	↔
Men with hypogonadism and prostate cancer	Serum PSA, prostate volume or symptoms (urine flow rate, voiding symptoms, prostate biopsy)	1	21	6	↔

Table 1 continued

Characteristics of study population	Outcome	Number of available RCTs	Number of enrolled subjects	Mean duration of RCT months (range)	Summary of observed effects
Men with hypogonadism and diabetes mellitus type 2 or Metabolic syndrome	Serum PSA, Prostate volume, IPSS	3	239	10 [7–12]	↔
Other parameters (for additional data see references [1, 42–48])					
Major depression	Improvement of depressive symptoms	5	210	7.6 (6–12)	↑
HIV/AIDS	Improvement of lean mass	2	82	21 (16–26)	↑

↔ no modification or conflicting results after TS; ↑ increased during TS; ↓ decreased during TS

majority of patients had a clinical condition of HG with markedly reduced T levels (< 8 nmol/L) or T levels between 8 and 12 nmol/L and symptoms of HG. A smaller proportion of patients showed comorbidities such as T2DM or MetS [9, 10, 54]. Only 23 % of 250 patients had an increase in prostate volume (assessed by digital rectal examination or prostate ultrasound scan) [6, 23, 55], whilst in the remaining it was within the normal range.

Values

The task force places high value on the recommendation that TS, when appropriately given to HG men, has no carcinogenic effect on an otherwise unaffected prostate gland.

Remarks

The effects of TS on the prostate gland are not such as to advise limiting its use, given its potential benefits on various cardiovascular, metabolic and sexual outcomes. TS may therefore be considered safe for the prostate gland in all patients without clinically evident PCa, as long as accurate screening is performed beforehand and adequate follow-up is performed.

Adverse effects

23. We recommend against using TS in patients with haematocrit higher than the upper limit of the normal range (1 ØØØØ).
24. We recommend monitoring blood parameters to avoid critical elevation of haematocrit, especially when using intramuscular T preparations (1 ØØØØ).
25. We suggest against using 17-alpha-alkylated derivatives of T. The available T preparations do not have negative effects on liver function [48] (2 ØØØØ).
26. We recommend against starting TS in HG patients who are attempting to father a child (1 ØØØØ).

27. We suggest against using TS in men with a known history of obstructive sleep apnoea (2 ØØØØ).

Evidence

TS induces a dose-dependent increase in haematocrit within 1 month [27, 28]. This effect is higher with short-acting than with long-acting, injectable T esters or transdermal preparations [33]. The increase is caused by both erythropoietin and the direct effect of T on bone marrow [56]. Fernandez-Balselles et al. [28] showed that T-treated men had a 3.15-times higher risk of developing erythrocytosis compared to placebo-treated controls, especially with intramuscular T formulations. However, this rarely results in thrombosis, as demonstrated by meta-analyses considering all cardiovascular events [1, 27, 28]. Nevertheless, frequent monitoring is necessary to avoid critically elevated levels, with 54 % considered the cut-off for suspension [48]. Polycythaemia reverts to baseline after T withdrawal. RCTs rarely report increased haematocrit as an adverse event of TS (Table 1). Some studies report a significant haematocrit increase with intramuscular TS [10, 57–59]. However, only a small number of HG patients were considered and haematocrit was not the primary endpoint.

The negative effect of TS on liver function is only associated with the use of alkylated 17α T formulations, which have already been withdrawn from the market. Long-term studies showing the liver effects of the currently used T preparations are lacking.

TS down-regulates the hypothalamus–pituitary axis, depressing LH and FSH and further decreasing endogenous T synthesis, thereby inhibiting sperm production [48]. Androgens have been actively studied for potential use in male hormonal contraception. The negative effect of T on fertility is transient and fully reversible, with a predictable course [60].

Few studies have considered the effects of TS on obstructive sleep apnoea syndrome (OSAS) in patients with

HG. One randomised, placebo-controlled study showed that intramuscular *T* undecanoate acutely worsened sleep hypoxaemia in patients with obesity and OSAS. An open-label study on five HG men reported worsened OSAS with intramuscular *T* enanthate [61]. However, Snyder et al. [62] did not find any change in respiratory distress index in 108 HG men treated with transdermal *T* for 36 months.

Few randomised, placebo-controlled trials indicate which adverse events resulted in patients dropping out of the study. In men treated with transdermal *T* erythema, pruritus and nasopharyngitis occurred in about 45 % of patients in both the study and control groups [10]. Transdermal approaches might increase the risk of transfer of *T* to others during close skin contact, although this was found unlikely in a randomised controlled study [63].

Values

There is enough evidence to recommend avoiding the use of TS in men with elevated haematocrit levels. To prevent this adverse effect, the task force gives a high value to monitoring haematocrit during treatment. Similarly, a high value is given to the negative effect of *T* treatment in patients requiring fertility. Few RCTs have evaluated TS in men with OSAS.

Remarks

There is no clear haematocrit threshold above which TS should be avoided or suspended, therefore, continuous monitoring of the individual risk profile (e.g. dehydration, hypercoagulability, smoking) is mandatory during *T* treatment. At the same time, any wish to start a family should be considered before starting TS. Finally, OSAS is a complex disease and generally has a multifactorial aetiology. In this context, the effect of TS is far from being understood and the decision to start the therapy depends on a careful evaluation of the patient's characteristics.

Conflict of interest All authors certify that they have no actual or potential conflict of interest in relation to this article.

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